REMARKS

Claims 113-119 are pending in this application. Claims 1-112 and 120-133 has been cancelled without prejudice or disclaimer. Claims 113 and 114 are amended to recite for clarity to recite that "the physically cross-linked hydrogel is formed without chemical cross-linkers, irradiation or thermal cycling." The amendment is fully supported by the specification (see for example, page 28, lines 18-19) and as described below. Therefore, no new matter is introduced. The Office Action is discussed below:

Withdrawal of Rejections:

Applicants thank the examiner for withdrawal of the alleged anticipation rejection based on Ottoboni *et al.* and the indefiniteness rejection in view of response filed on August 18, 2006.

Anticipation and Obviousness Rejections:

On pages 2-3 of the Office Action, the examiner has maintained the rejection of claim 113 allegedly as being anticipated by Hyon (US 4,663,358), Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), Yamauchi (JP 03215417), or Okamura (JP 04338326).

The examiner also has maintained the rejection of claims 114-119 allegedly as being anticipated by or, in the alternative, as being obvious over Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), or Okamura (JP 04338326).

Applicants respectfully disagree with the examiner and reiterate that "injectable hydrogel" is not expressly or inherently disclosed in any of the cited art. Applicants refer the examiner to MPEP § 2131 (Rev. 5, August 2006) that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

On page 3 of the Office Action, the examiner asserted that the applicants provide insufficient evidence to support the conclusionary statements that the "[f]reeze-thaw process does not permit preparation of an injectable formulation" and "[the] Hyon method can not yield an injectable hydrogel." In response, applicants herewith submit a declaration by Dr. Stephen Spiegelberg demonstrating why none of the methods described in the cited references would yield an injectable hydrogel (see attached Declaration of Dr. Stephen Spiegelberg).

Regarding Hyon *et al.*, Ku *et al.*, Yao *et al.*, and Okamura, on page 3 of the Office Action, the examiner noted that the features, such as "a hydrogel without the freeze-thaw treatment", are not actually recited in the claims. Applicants respectfully disagree with the examiner and submit that the claims are directed to a composition, therefore recitation of the steps for making the composition is not required for a composition claim. Applicants note that the examiner reasoning was directed to the methods used in the cited references that involve the freeze-thaw treatment. In response, applicants indicate that the instant methods do not involve the freeze-thaw treatment and yield an "injectable hydrogel", which is not possible by the methods disclosed in the cited references. See attached Declaration of Dr. Stephen Spiegelberg, Example 1 and 2. Moreover, the cited references do not disclose the claim element "injectable hydrogel." Therefore, the cited references do not anticipate and/or make the claimed invention obvious. However, without acquiescing in the rejection, in order to expedite the prosecution, applicants amend claims 113 and 114 for clarity, without prejudice or disclaimer, to recite that "the physically cross-linked hydrogel is formed without chemical cross-linkers, irradiation or thermal cycling." That is, the hydrogel is formed without thermal cycling to freeze and thaw the hydrogel. Applicants further explain that the lack of such thermal cycling allows the instantly claimed hydrogels to be "injectable", unlike the gels prepared by the methods disclosed in the cited references. The amendment is fully supported by the specification (see specification, for example, page 5, line 22 through page 6, line 13; page 11, lines 15-18; page 13, line 19-29; page 25, lines 23-29; and page 28, lines 18-19). Withdrawal of the alleged anticipation and obviousness rejections is therefore requested.

Regarding Yao *et al.*, on page 3 of the Office Action, the examiner refers to col. 9, lines 58-67, and states that depending on the end use, the hydrogel can be repeatedly freeze and thawed to increase its viscosity. Thus, according to the examiner's belief, after one cycle, the hydrogel would still be at least injectable. Applicants respectfully disagree with the examiner and refer to the Declaration of Stephen Spiegelberg that the hydrogel produced by a single cycle freeze-thaw thermal cycling treatment is not injectable (See attached Declaration of Dr. Stephen Spiegelberg, Example 2).

Regarding Tanihara *et al.*, on pages 3-4 of the Office Action, the examiner asserted that regardless of the purpose of including the salts in the composition Tanihara (as gellants and/or therapeutic / modulus modifier), the claim only requires that they are present. The examiner also asserted that the statement that "[the] Tanihara [hydro]gel is not injectable" is conclusionary and not supported by evidence, either provided by or pointed to by applicant. Applicant respectfully disagree with the examiner and reiterate that Tanihara describes a chemically modified repeat unit to improve heat resistance and the resulting material is not a PVA hydrogel. The material is used as wound dressing thus, is not an injectable hydrogel (see col. 3, line 64 through col. 4, line 21; see col. 16, line 48 through col. 21 line 47, for process of making the modified gel and its characteristics usable as wound dressing but not as an injectable hydrogel). Applicants point out that the term "injectable hydrogel" or "injectable" use of the gel is not expressly or inherently disclosed in the Tanihara disclosure. Therefore, Tanihara cannot anticipate the claimed invention.

Applicants further elaborate that Tanihara disclosure is not relevant to the claimed invention as it does not disclose a PVA hydrogel according to the instantly claimed invention. Tanihara does not describe a PVA hydrogel because the commonly understood definition of a PVA polymer is one with the majority of monomeric groups consisting of–CH2-CHOH-, depending on hydrolyzation of saponification level. The name, PVA is an acronym for poly(vinyl alcohol) and therefore technically requires a molecule that is composed of vinyl alcohol monomers. The "PVA" described by Tanihara contains structural units at mole fractions of 0.05 to 0.5 of the formula I and/or

formula II in that patent, and is thus termed a 'copolymer' by those familiar in the art, and cannot be simply described as "PVA" (see col. 3, line 64 through col. 4, line 21). Tanihara claims a wound dressing material of hydrogel containing HA or HA-salt (see claims 1 & 2). The material described by Tanihara is however not a PVA polymer, and is instead a molecule with a specific pendant group (see formula I). The examiner points out that there are other ingredients added to this gel but since Tanihara makes a point of not using true PVA, and the added ingredients are at relatively low concentrations, thus does not teach an injectable hydrogel (see col. 16, line 48 through col. 21 line 47, for process of making the modified gel and its characteristics usable as wound dressing but not as an injectable hydrogel).

On page 4 of the Office Action, the examiner states that "the hydrogel is formed from covalently-bonded PVA through ionizing radiation" is not "explicitly" found in Yamauchi *et al.* In response, applicants refer to Yamauchi disclosure, which clearly describes under the "constitution" that the gel is "an aqueous solution of polyvinyl alcohol containing hyaluronic acid which is one kind of mucopolysaccharides or salt thereof is irradiated with ionized radiation to form a water-containing gel...." (see Yamauchi *et al.* Japanese patent JP403215417A, cover page under "constitution"). Applicants also refer that according to Yamauchi disclosure, "a hydrogel is formed by irradiating an ionized radiation on an aqueous solution of polyvinyl alcohol containing hyaluronic acid and its salts to form cross-links among polyvinyl alcohol molecules and make it into a three-dimentional network structure." (see Yamauchi *et al.* Japanese patent 03-215417, for example, paragraph bridging pages 8 and 9).

Applicants further note that ionizing radiation is generally known to covalently link PVA to form a gel (see for example, Hyon *et al.* col. 1, line 41-45). Thus, Yamauchi "explicitly" discloses cross-linking of the gels by ionizing radiation, which results in cross-linking to form a three-dimentional network structure, and requires that its gel constitution be exclusively cross-linked by ionizing radiation.

Applicants reiterate that the Yamauchi's gel formulation cannot be used in an "injectable" form, because a radiation source is required for the final gelation process. Yamauchi gels are used for drug release and the salts are present to control pore size,

which aids in drug release rate. The salts are not used in the Yamauchi gels to form the hydrogel, however. (see Yamauchi *et al.* Japanese patent 03-215417, for example, pages 6-11). In contrast, the instant invention forms a hydrogel through physical cross-linking as induced by the presence, for example, of the salt, and does not use chemical cross-linkers, irradiation or thermal cycling. Applicant indicate that the hydrogel formation or the "gelation", according to the claimed invention, refers to the formation of permanent physical cross-links due to the crystallization of the PVA (see specification, for example, page 24, lines 8-16). For example, according to the invention, hydrogel can be produced by controlling the diffusion of the second solvent (NaCl or methanol) into a PVA solution to produce a homogenous, physically cross-linked structure (see specification, for example, page 6, lines 19-22; page 24, lines 8-16; and page 28, lines 18-19).

However, without acquiescing in the rejection, in order to expedite the prosecution, applicants amend claims 113 and 114 for clarity, without prejudice or disclaimer, to recite that "the physically cross-linked hydrogel is formed without chemical cross-linkers, irradiation or thermal cycling." That is, the hydrogel is formed without radiation cross-linking. Applicants further explain that the lack of ionizing radiation treatment allows the instantly claimed hydrogels to be "injectable." The amendment is fully supported by the specification (see specification, for example, page 6, lines 19-22; page 11, lines 15-18; page 13, line 19-29; page 25, lines 23-29; and page 28, lines 18-19).

Therefore, Yamauchi does not anticipate the claimed invention.

Further, on page 4 of the Office Action, the examiner contends that "with a big enough injector, any gel/hydrogel can be injected." Applicants remind the examiner that the hydrogel is intended for injection into humans or other living subjects, and thus the examiner is not reasonably construing the claims. In general, injectability requires a liquid material. Applicants note that all of the cited references, including Yamauchi, describe manufacture of the hydrogels *in vivo*, and can thus not formally meet the requirement of injectability of the device. Hydrogels are very deformable due to their high water content, but if a solid hydrogel was to be "injected" through a narrow needle,

it must either return to its original shape after deforming and stretching during "injection", or break in the process. This behavior is different from a liquid that can be injected, which does not need to stretch during injection, and which can fully fill any cavity after injection. A large enough "injector" to accommodate the solid hydrogel cannot be considered an injector, and is more properly defined as an inserter. Applicants also refer to the experimental results that the hydrogels made with freeze-thaw treatment are not injectable and did not extrude through 4 mm orifice (See attached Declaration of Dr. Stephen Spiegelberg, Examples 1 and 2).

Regarding the anticipation and obviousness rejections, on page 4 of the Office Action, the examiner contends that generic disclosure of the claimed hydrogel is present in the cited reference. Applicants continue to disagree with the examiner that the generic disclosure of the cited references do not expressly or inherently disclose an "injectable hydrogel." The hydrogels disclosed in the cited references are not injectable and the methods disclosed therein also do not produce "injectable hydrogel" (See attached Declaration of Dr. Stephen Spiegelberg, Examples 1 and 2). The "injectable hydrogels" recited in claims 113-119 are characteristically, physically as well as chemically, different from the hydrogels disclosed in any of the above cited references. Therefore, the claimed "injectable hydrogel" is not expressly or inherently disclosed in the cited references.

The examiner points out, on page 4 of the Office Action, that "substantially free of chemical crosslinkers" is not the same as "free of chemical crosslinkers." Applicants indicate that the claimed invention relates to an injectable physically cross-linked hydrogel. Any hydrogel that is manufactured using freeze-thaw or radiation crosslinking is not injectable (see above discussion and attached declaration of Dr. Stephen Spiegelberg) since the hydrogel is made into a solid hydrogel *in vitro*. Thus, the claimed invention relates to injectable and physically cross-linked hydrogel, which is also substantially free of chemical crosslinkers.

Applicants further note that, without acquiescing in the rejection, in order to expedite the prosecution, claims 113 and 114 are amended for clarity to recite that "the physically cross-linked hydrogel is formed without chemical cross-linkers, irradiation or

thermal cycling." That is, the hydrogel is formed without use of any chemical cross-linkers. Applicants further explain that the lack of chemical cross-linking treatment allows the instantly claimed hydrogels to be "injectable." The amendment is fully supported by the specification (see specification, for example, page 24, lines 8-16; and page 28, lines 18-19).

Withdrawal of the alleged anticipation and obviousness rejections is therefore solicited.

In order to assist the examiner in further distinguishing the claimed invention from the cited references, applicants provide the following explanation:

According to the examiner the PVA hydrogels with salts added are taught by Tanihara, Ku, Yao or Okamura, but none of the cited references are relevant to the claimed invention. Applicants further clarify that:

As discussed above, Tanihara does not describe an injectable PVA hydrogel rather discloses a wound dressing material containing a modified PVA hydrogel, which is not injectable. Thus, additions of other ingredients, such as salts, to Tanihara gel would not result into an injectable hydrogel according to the instantly claimed invention. Tanihara describes a method of making a modified PVA solution by dissolution in an organic solvent, which can then be processed by immersion in water or some other solvent, or by crosslinking or freeze-thawing. Therefore, the final article is a solid hydrogel, which cannot be injected (see col. 16, line 48 through col. 21 line 47, for process of making the modified gel and its characteristics usable as wound dressing but not as an injectable hydrogel).

Ku describes a cryogel which requires freezing, thus cannot be injected as a liquid. This formulation may include isotonic saline to "prevent osmotic imbalances" but the concentrations are well below those according to the invention. Ku describes a PVA hydrogel that is manufactured by freezing. Freeze-thaw manufacture of a hydrogel by definition produces a solid hydrogel *in vitro* which cannot be subsequently injected, even with a single freeze-thaw cycle.

Yao describes a method for making a porous freeze-thaw hydrogel including a dopant which is subsequently removed. Dopants can be salts, but the dopant concentrations are only 3-8 wt%, and the Yao device is made using the freeze-thaw process. The latter step again precludes the ability to inject the formulation as a liquid or to form the gel *in vivo*. Yao also describes manufacturing a PVA hydrogel by freezing (see col. 9, line 58). The examiner believes that Yao teaches multiple freeze-thaws, which result in increased viscosity, "thus after one cycle hydrogel is injectable". Applicants note that there is no support in the Yao *et al.* (US 6,268,405) for the examiner's statement that "Yao *et al.* teach that depending on the end use, the hydrogel can be repeatedly freeze-thawed to increase its viscosity." The freeze-thaw process results in a continuous network of polymers (see Yao *et al.* where it is considered that an "infinite network" of polymer chains in a solvent (see P.J. Flory, "Principles of Polymer Chemistry" (1986), copy of relevant pages attached). The pre-gel polymer solution is a viscoelastic liquid and flows under steady shear. However, as the polymers in the solution crosslink form a continuous network. The solution reaches the "gel point" when the network attains a mechanical strength with an infinite steady shear viscosity. Once a continuous network is formed, which is required for the system to become a considered hydrogel, the network becomes strongly elastic and non-injectable. In contrast, as discussed above, the instant invention forms a hydrogel through physical cross-linking as induced by the presence of the salt, which do not use chemical cross-linkers, irradiation or thermal cycling. Applicant indicate that the hydrogel formation, according to the claimed invention, refers to the formation of permanent physical cross-links due to the crystallization of the PVA. This is in contrast to the previously known processes in which gelation refers to the point at which the polymer associates, and need not be followed by the crystallization that forms a permanent link (see specification, for example, page 24, lines 8-16). For example, the claimed hydrogels are produced by controlling the diffusion of the second solvent (NaCl or methanol) into a PVA solution to produce a homogenous, physically cross-linked structure (see specification, for example, page 6, lines 19-22; page 24, lines 8-16; and page 28, lines 18-19).

Okamura describes a hydrogel formed from PVA plus ethanol, salt, drugs, urea and face powder dissolved and frozen to form hydrogel sheet. The latter step again precludes the ability to inject the formulation as a liquid or to form the gel *in vivo*. Okamura also describes a PVA hydrogel containing multiple species but the hydrogel is manufactured by freezing.

Hyon uses a mixed solvent of water and water miscible organic solvent which is then subsequently cooled to below room temperature to forms a gel. Instantly claimed invention do not need to reduce the temperature below the room temp, which causes gelation (see Abstract). If manufactured in this way, it cannot be injectable as it forms a solid construct, and the sub-ambient cooling step also precludes gelling *in vivo*. In the details of the invention, Hyon describes that the lower the temperature the better, (see col. 3, lines 25-32) but at no point Hyon claims that the material can be molded or injected during this gelation step. All of Hyon's examples indicate freezing step to make the hydrogel (see col. 4-7).

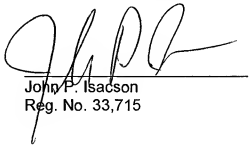
As discussed above, Yamauchi describes a PVA hydrogel made by irradiating a PVA solution containing other ingredients. The irradiation process precludes the ability to form the gel *in vivo* or to inject it as a liquid. Yamauchi discloses a PVA hydrogel that is crosslinked by radiation, therefore cannot be injected as a liquid.

In view of the above clarifications, arguments, amendments to claims 113-114, and the declaration of Dr. Stephen Spiegelberg, applicants respectfully request the withdrawal of all outstanding anticipation and obviousness rejections.

REQUEST

Applicants submit that the claims 113-119 are in condition for allowance and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 416-6800 should there be any questions.

Respectfully submitted,



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